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Rapid Initiation of Antiretroviral Therapy after HIV Diagnosis

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Abstract

Roughly, 38 million people are living with HIV worldwide. Despite the success of antiretroviral therapy (ART) for suppressing virus replication and restore immunity in infected persons, the HIV epidemics are not controlled globally. Each year 1.8 million new HIV infections occur. This rate has declined only slightly during the past decade, despite huge efforts for expanding ART coverage, pre- and post-exposure prophylaxis, and stopping vertical transmission. To achieve the United Nations Programme on HIV/AIDS goals of 95-95-95 by 2030, renewed efforts and innovative strategies must be undertaken. The source of most new HIV infections is people unaware of their HIV-positive status and/or not linked to care. Thus, efforts for unveiling HIV positives and, especially, rapid initiation of ART and retention in care would be the most effective interventions for halting HIV spreading globally. In certain settings, access to point-of-care diagnostic tests and immediate start of ART (even the same day) must be implemented at large scale. Selection of the most convenient ART to be prescribed empirically is an important caveat to minimize the risks of treatment failure. Ideally, it must be easy to take, coformulated as single-tablet regimen (STR), well tolerated, with no requests for prior human leukocyte antigen testing, depict few drug interactions, keep activity against transmitted drug-resistant viruses, remain efficacious in patients with elevated HIV-RNA, and/or low CD4 counts, and when present, suppress hepatitis B coinfection. At this time, the coformulation of darunavir, cobicistat, emtricitabine, and tenofovir alafenamide (Symtuza®) is the only regimen that has been evaluated in a Phase 3 trial as "test-and-treat" strategy. Results at 48 weeks in the DIAMOND study are reassuring, as more than 90% of individuals achieve undetectable viremia. **(AIDS Rev. 2019;21:55-64)**

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Key words

Antiretroviral therapy. Test and treat. Rapid initiation. Early diagnosis. Drug resistance. Darunavir.

Introduction

The advent of highly active antiretroviral therapy (ART) has represented a major breakthrough in the HIV/AIDS field. The use of ART prevents HIV disease progression and restores immunity in almost all HIV patients[1-3]. In addition, ART stops further transmissions, as a result of reducing infectivity of carriers (treatment as prevention [TAP])[4]. More recently, the

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use of antiretrovirals by uninfected individuals at risk (pre-exposure prophylaxis [PrEP]) has shown to drastically reduce the chances of HIV acquisition[5].

Despite all these tremendous advances, the figures for the HIV pandemic remain dreadful, with estimates of 38 million people living with HIV worldwide and 1.8 million new infections occurring each year. Looking at this scenario, the call from the United Nations Programme on HIV/AIDS (UNAIDS) for <200,000 new HIV infections globally by 2030 is quite challenging. Moreover, the achievement of 95-95-95 goals by 2030 seems too far in the horizon (Fig. 1), taking into account the current figures[6]. Clearly, new innovative strategies and renewed efforts should be undertaken. Table 1 summarizes the most important fronts of action for controlling the HIV pandemic globally.

Current ART recommendations

Since 2012, most international ART guidelines recommend initiation of ART in all newly diagnosed persons with HIV infection regardless of CD4 counts, to reduce the risk of AIDS-related and non-AIDS-related events[1-3] as well as transmission to uninfected partners[4]. Yet, in 2016, only 63% of patients with HIV-1 in the United States were on treatment and 51% of patients were virologically suppressed[7].

Two major studies, Strategic Timing of Antiretroviral Treatment (START)[8] and TEMPRANO[9], clearly established the benefit of universal ART for HIV infection. These studies pushed the rationale for expedited early ART initiation. However, they did not specify the time frame for early initiation of ART. In the START trial[8], the study participants did not receive same-day ART, although 98% of those in the immediate start arm commenced ART within 2 months after HIV diagnosis. The lag of time between diagnosis and ART initiation was not specified in TEMPRANO.

Nowadays, the Department of Health and Human Services (DHHS) guidelines recommend that certain laboratory testing be performed before starting ART to help guide initial treatment selection. However, some testing (e.g., drug resistance or human leukocyte antigen [HLA]-B*5701) may require several days or weeks for results, contributing to poor retention rates and delayed initiation of ART[1].

Guidelines from the International Antiviral Society-USA now explicitly state that ART should commence immediately after diagnosis[2]. Likewise, the European AIDS Clinical Society guidelines recommend initiation of ART as soon as possible, stressing further patient's readiness[3].

Rapid ART initiation

In rapid initiation models of HIV care, ART is started (sometimes on the same day as diagnosis) before the availability of baseline laboratory assessments. More importantly, these models have shown benefits in retention in care, morbidity, mortality, and time to virologic suppression[10-12].

The World Health Organization (WHO) recommends rapid initiation of ART for all persons newly diagnosed with HIV-1 infection[13]. In contrast, the United States DHHS still considers this approach as investigational, given that most supporting evidence has been generated overseas. However, DHHS guidelines recognize the importance of prompt ART initiation for particular patient populations such as acute infection, pregnant women, and coinfection with hepatitis B/C[1].

Health-care providers have less clinical information available in a rapid initiation model of care, so it is important to consider a regimen's effectiveness in the setting of possible transmitted drug resistance, its safety profile, and the patient's ability to adhere to the regimen. An optimal ART regimen for use in this setting should ideally have a high barrier to resistance, be a single-tablet regimen (STR), and be abacavir sparing (avoiding HLA typing requests)[11,12]. Table 2 records the most important features that an ideal ART regimen should fit to be used empirically in rapid initiation models.

Who are the source of new HIV infections?

A recent study from the Center for Disease Control examined in detail the source of new HIV infections in the United States[7]. For this purpose, the HIV population was split out into five categories. First, individuals recently infected that were unaware of their HIV status. Second, individuals with chronic HIV infection that was undiagnosed. Third, persons that had been diagnosed for a while but that for some reason did not take antiretrovirals. Fourth, patients on medical care that was failing ART, often due to poor drug adherence. Last, patients those were treated and suppressed.

Figure 2 shows the estimated source of these contagions, taking into account the transmissibility of the five distinct HIV populations mentioned above, which was directly proportionated to their average viral load and risk behaviors. Overall, 80% of new HIV infections came from persons that were not aware of their HIV positivity

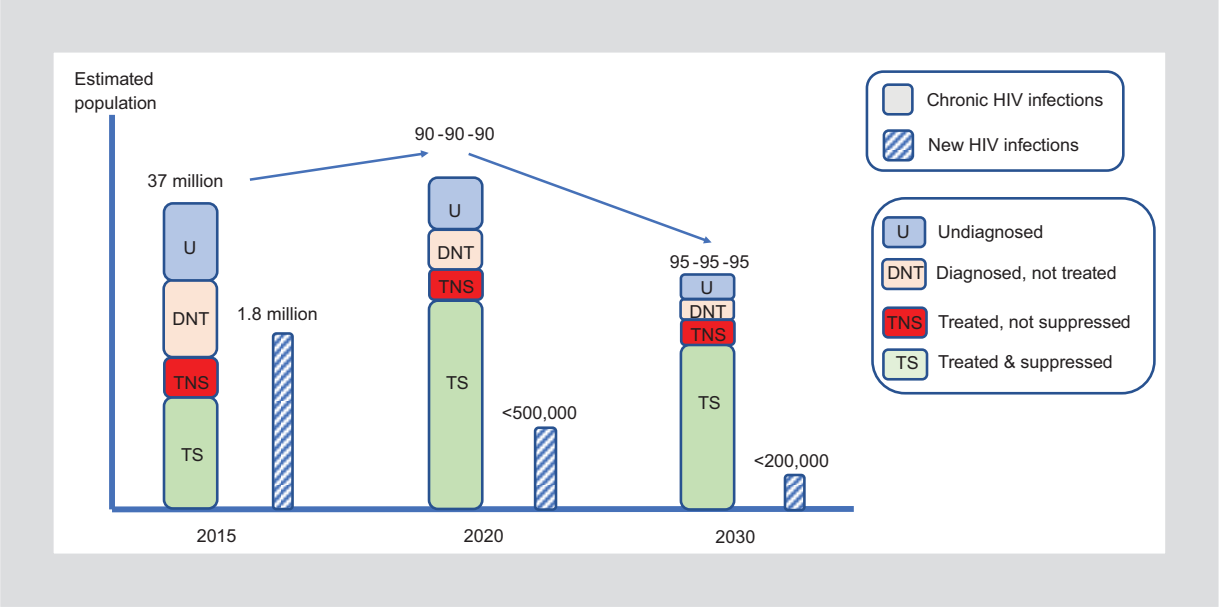

Figure 1. *The United Nations Programme on HIV/AIDS goals for the global HIV epidemics.*

or that did not take ART despite knowing it. The latest group represented 22% of the estimated HIV population in the United States, underscoring the fact that HIV infection remains asymptomatic for nearly one decade in carriers and that some people may choose to stay off medical care during that timeframe. In addition to this subset of individuals diagnosed but untreated, another 15% were unaware of their HIV status whereas continuing having risk behaviors, mostly sexual contacts[7].

In most other regions of the world, gaps in the HIV cascade of continuum of care are even greater. Clearly, expanding HIV screening and ART coverage for HIV positives must be prioritized. Despite clear evidence showing that current ART works very well, still a relatively low proportion of HIV persons is benefited globally. The development of easy to make HIV tests, including point-of-care tools, as well as efforts to initiate ART as soon as possible after HIV diagnosis, even within the same day, must move forward. Any deferral of ART initiation following HIV diagnosis translates into lower retention in care[14]. At this time, the "test-and-treat" strategy seems to be the most efficient way to guide the path toward global HIV control.

While PrEP works for HIV prevention in the subset of individuals engaged in high-risk sexual behaviors, it must be acknowledged that this population is relatively small globally[15]. As the treatment of HIV positives is much more cost effective than PrEP, communities would largely benefit from considering ART as prevention (TAP) as the priority. Furthermore, rebounds in

Table 1. Major gaps for controlling the HIV epidemics globally

– Easy access to point-of-care diagnosis
– Universal and early provision of ART to all newly diagnosed HIV positives
– Ensuring everywhere HIV antenatal testing and treatment for halting mother-to-child transmission
– Improving sustained care and retention of all HIV positives
– Expanding pre-exposure prophylaxis to uninfected persons at risk

ART: Antiretroviral therapy

Table 2. Ideal regimen for empirical early ART initiation

– Coformulation as single-tablet regimen
– Well tolerated
– Few drug interactions
– No prior HLA typing
– High barrier to resistance
– Efficacy unaltered in patients with low CD4 counts and/or high viral load

ART: Antiretroviral therapy, HLA: Human leukocyte antigen

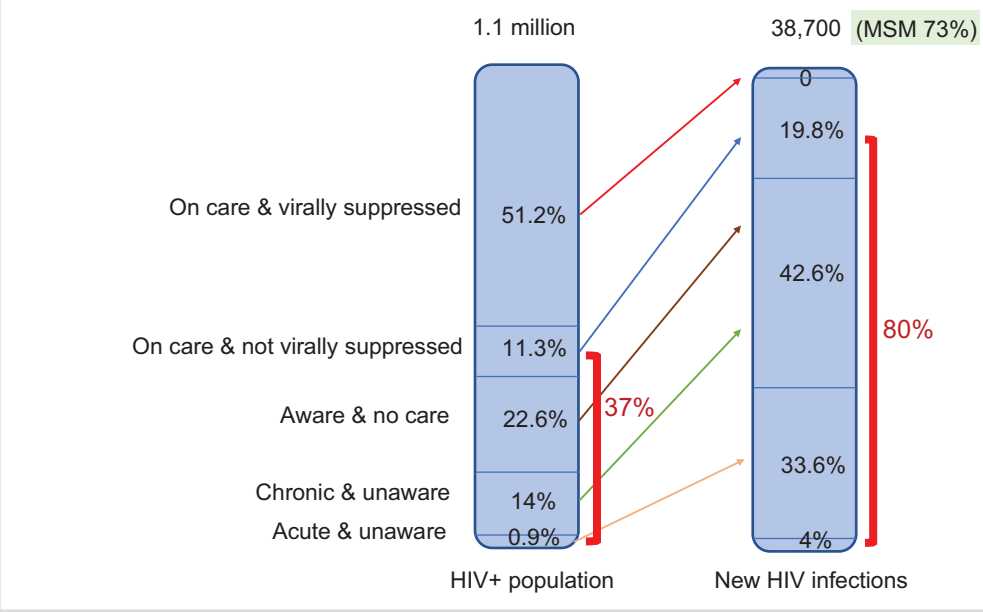

Figure 2. *Estimates for HIV transmission rates in the United States*[7].

sexually transmitted infections associated with the loss of HIV/AIDS fear in PrEP users are an unwanted effect of giving drugs without implementing proper sex education to content high risky behaviors[16]. Therefore, efforts and funding should be concentrated in expanding early and universal ART coverage[15], in line with the Prevention Access Campaign that explicitly reads U=U (undetectable means untransmittable)[17].

"Test-and-Treat" trials

Early initiation of ART in most poor countries is mostly driven by high rates of late presentation of HIV patients, often with CD4 counts below 200 cells/mm^3 and/or overt AIDS clinical manifestations. On the other hand, loss to follow-up on HIV diagnosis is common, especially for asymptomatic individuals. Both findings affect negatively outcomes when unnecessary ART delays occur.

The rapid initiation of ART following HIV diagnosis was evaluated in four major studies conducted in Sub-Saharan Africa and Haiti[18-21]. All were randomized trials that compared rapid start of ART versus the standard of care. Table 3 records the proportion of patients with viral load suppression and retention in care at week 48. Uniformly, all studies showed that rapid start of ART was associated with improved outcomes, which indirectly reflects that starting ART in many developing countries is a lengthy and burdensome process that often imposes long waits and multiple clinic visits on patients. At the last Conference on Retroviruses and Opportunistic Infections, a large open-label single arm study conducted in Haiti confirmed these previous findings[22]. In particular, "same-day" ART initiation using empirical medication seems to be the most feasible approach. Rapid initiation of ART in developing regions may additionally halt further sexual HIV transmissions.

The evidence for the benefit of rapid initiation of ART in Western countries has been demonstrated in a few studies[23-26]. The advantages were originally recognized in the US-based study conducted at 45 clinics, in which early ART (initiation within 2 weeks) in patients presenting with opportunistic infections was associated with slower progression to AIDS and lower death rates[23].

There are significant differences in the management of HIV persons in developed countries compared to low-middle-income countries. HIV diagnosis tends to be made earlier when CD4 counts are above 350 cells/mm^3. In addition, loss to follow-up is not a big concern in most Western countries, except for some particularly vulnerable populations such as illegal immigrants, injection drug users, and homeless. In those groups, disengagement from care is frequent and same-day ART initiation may add considerable value.

Cost-effectiveness is, nowadays, an important consideration for designing health plans. Scientists from Janssen recently examined the impact of early ART

Table 3. Major studies evaluating "test-and-treat" ART approaches

Study	Region	ART initiation (Rapid arm)	Results (at 12 months)		
				Rapid arm	Standard arm
RapIT[18]	South Africa	<90 days	n	187	190
			VL suppression (%)	64	51
			In care (%)	81	64
START ART[19]	Uganda	<4 days	n	347	356
			VL (%)	53	44
			In care (%)	80	72
Koenig, et al.[20]	Haiti	Same day	n	206	208
			VL suppression (%)	66	58
			In care (%)	84	84
Labhardt, et al.[21]	Leshoto	Same day	n	137	137
			VL suppression (%)	50	34
			In care (%)	67	43

ART: Antiretroviral therapy

initiation in a large USA database[26]. They compared outcomes during the past 5 years in commercially-insured patients with those belonging to the Medicaid system. Among 9351 individuals on ART attended with private insurance, 48% of patients had initiated ART within the 1st month, 72% within 2 months, and 94% within 12 months. These figures were 24%, 36%, and 64% for Medicaid patients. The rate of opportunistic infections, neuropsychiatric complications, and other HIV-associated comorbidities during the past 6 months before beginning ART was higher among Medicaid than privately insured patients. Accordingly, overall health costs, balancing pharmacy versus medical care, largely favored rapid initiation of ART (Fig. 3).

In a separate analysis of costs of health resource utilization on 21,516 Medicaid patients with HIV, Janssen investigators concluded that lower emergency room and outpatient visit costs seen recently in Medicaid could be related to changes in treatment guidelines and in the provision of health-care services. Furthermore, increased availability of STR and newer ART with improved tolerability and safety profiles could have contributed to cost reductions[27].

In a large meta-analysis led by the WHO, clinical trials and observational studies were retrospectively analyzed. Rapid initiation of ART was defined as within 14 days of HIV diagnosis. Significant increases were noticed for viral suppression and retention in care at 12 months[11]. The authors concluded that accelerated ART initiation can lead to improved clinical outcomes and might be of particular benefit in settings where extensive patient preparation before starting ART results in long delays. Based on these findings, the WHO recommended accelerated ART initiation, including same-day ART start.

The current evidence favors immediate ART initiation in HIV pregnant women and HIV individuals presenting with acute infection, HIV-related clinical manifestations, and low CD4 counts or coinfected with hepatitis B/C viruses. Moreover, beyond these situations, rapid start of ART in asymptomatic HIV persons may shorter the time to achieve virological suppression and in this way reduce the risk of HIV-associated complications and onward transmission. Fig. 4 shows the time to viral load suppression in persons recently diagnosed with HIV recruited in the RAPID trial[28]. Median time to viral suppression was 1.8 months using the RAPID intervention, 4.3 months for those treated following the universal guidelines, and 7.2 months for those treated following the CD4 count threshold guidelines. The study also noticed an advantage for using protease inhibitors

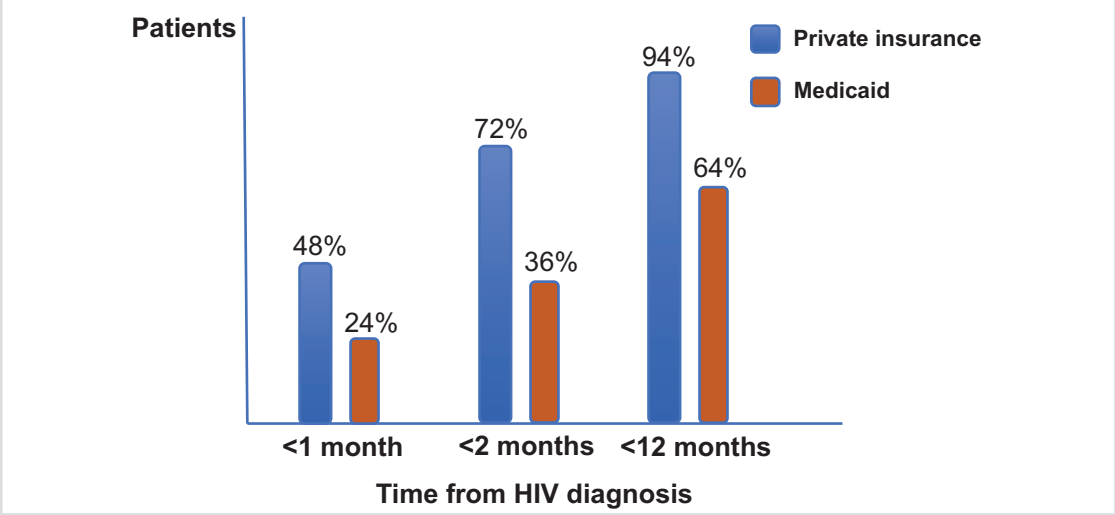

Figure 3. *Initiation of antiretroviral therapy in the United States according to health system*[26].

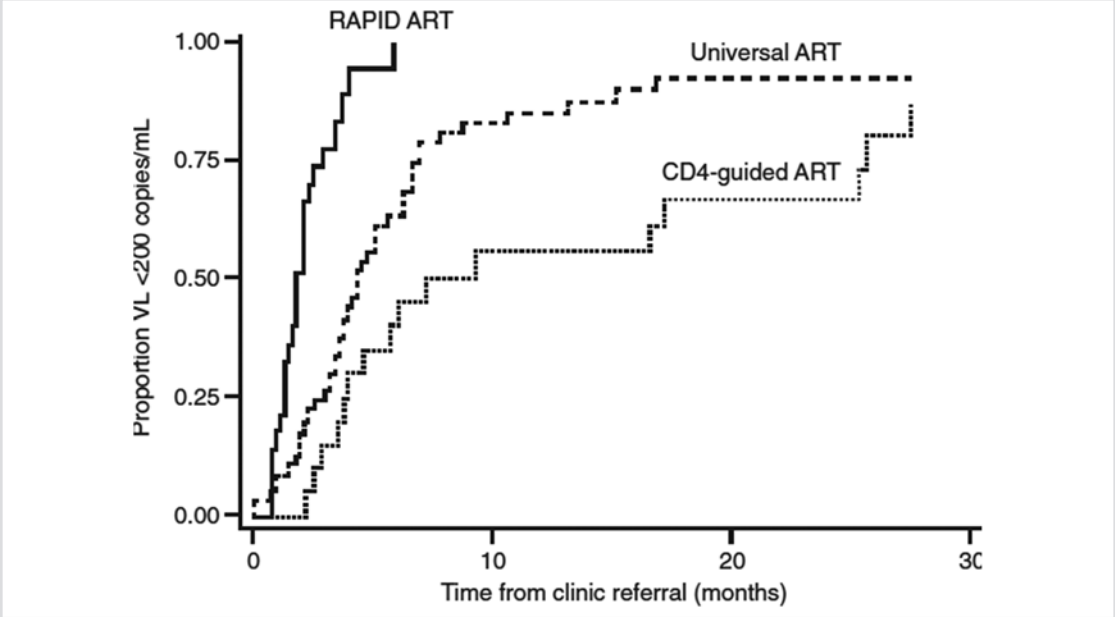

Figure 4. *Time to viral suppression in persons newly diagnosed with HIV (RAPID program)*[28], *by antiretroviral initiation strategy.*

(PIs) over other drugs when drug resistance testing is not available and suspicion exists about transmitted drug-resistant viruses. The authors highlighted that offering empiric treatment would demand improved education of practitioners maximizing efficacy of ART without risks[28].

Darunavir/Cobicistat/Emtricitabine/ Tenofovir Alafenamide (D/C/F/TAF)

D/C/F/TAF 800/150/200/10 mg (Symtuza®) is an oral, once daily STR approved for the treatment of drug-naïve and drug-experienced, suppressed patients with

HIV-1 infection. In the Phase 3 AMBER study of treatment-naïve patients, D/C/F/TAF was non-inferior to control for virologic response, Food and Drug Administration (FDA) snapshot, at week 48 (91.4% and 88.4%, respectively)[29]. In the Phase 3 EMERALD study of treatment-experienced, virologically suppressed patients, D/C/F/TAF was non-inferior to control for cumulative virologic rebound through week 48 (2.5% and 2.1%, respectively). Again, by FDA snapshot, virologic response rates were 94.9% and 93.7%, and virologic failure rates were 0.8% and 0.5% with D/C/F/TAF and controls, respectively[30]. In both studies, D/C/F/TAF was well tolerated with an improved renal/bone safety profile versus controls[31].

Darunavir has demonstrated a high barrier to resistance and is recommended in most international guidelines as an initial ART in cases, in which resistance testing records are unavailable or when ART needs to be started before availability of resistance testing results[31]. The unique characteristically high resistance barrier of boosted DRV makes this drug the ideal candidate when ART wants to be administered empirically, without information coming from baseline drug resistance testing.

The DIAMOND trial

It is the first Phase 3 study that has examined the efficacy and safety of a STR in a rapid initiation model of care. The study design was as open-label, single-arm, prospective, and multicenter trial conducted in consecutive newly diagnosed HIV-1 adults in the United States (ClinicalTrials.gov: NCT03227861)[32].

Individuals with certain known AIDS-defining conditions that could result in potentially life-threatening immune reconstitution syndromes (IRISs) on exposure to potent ART were excluded from enrollment. Likewise, persons with known advanced liver and/or severe renal insufficiency were excluded from the study. In contrast, individuals with prior use of tenofovir/emtricitabine as PrEP could be recruited in the study. Eligible patients (HIV diagnosis within 2 weeks) were immediately enrolled and started on D/C/F/TAF within 24 h of the screening and/or baseline visit and before the availability of the laboratory information.

A total of 109 patients were enrolled in the study. Overall, 87% were men, 32% Black/African-American, 25% had plasma HIV-RNA ≥100,000 copies/mL, and 21% had CD4 counts <200 cells/mm^3. All these features highlight the difficult-to-treat profile of the DIAMOND study population. Median time between HIV-1 diagnosis and screening/baseline was 5 (range, 0-14) days and 31% of patients were enrolled within 48 h of diagnosis.

No darunavir resistance-associated mutations (RAMs) were observed among patients with available genotype data at screening/baseline. All patients had full genotypic susceptibility to darunavir and tenofovir; two patients had emtricitabine RAMs (M184M/I and M184M/V). Among patients with a primary PI RAM, three had L90M, one had M46L, and one had Q58E. Five patients were found to have a transmitted secondary integrase inhibitor mutation at position 97.

Overall, 97 (89%) patients completed the study. By week 48, 12 (11%) patients had discontinued (three due to protocol-defined safety stopping rules, one withdrawal due to adverse events, four lost to follow-up, one protocol violation, one withdrawal of consent, and two for other reasons). No patients discontinued due to resistance stopping rules (Fig. 5).

Efficacy

In an intent-to-treat analysis at week 48, 92 of 109 (84%) patients had achieved HIV-RNA <50 copies/mL. Using the FDA snapshot algorithm at week 48, 92 of 96 (96%) patients had achieved HIV-RNA <50 copies/mL; the remaining four patients all had HIV-RNA <200 copies/mL. These figures are particularly relevant given the difficult baseline characteristics of the study population including high proportion of individuals with HIV-RNA above 100,000 copies/mL, low CD4 counts, and Black African-Americans. No patients experienced virological failure and there were no study discontinuations due to lack of efficacy.

No patients were eligible for post-baseline resistance testing. At week 12, 85 of 102 (83%) patients had achieved HIV-RNA <200 copies/mL and, by week 24, 96 of 98 (98%) had achieved this threshold (Fig. 6). The mean CD4 counts were 413 cells/mm^3 at screening/baseline and 628 cells/mm^3 at week 48.

Safety

Most adverse events were Grade 1 or 2. There were no serious adverse events or Grade 4 related to D/C/F/TAF, and there were no deaths. One patient discontinued due to allergic dermatitis, pyrexia, and lip swelling, all of which resolved after drug discontinuation. There were no IRIS cases. Few Grade 3 and 4 laboratory abnormalities occurred: increased bilirubin in three patients, increased ALT in three patients, and increased AST in five patients.

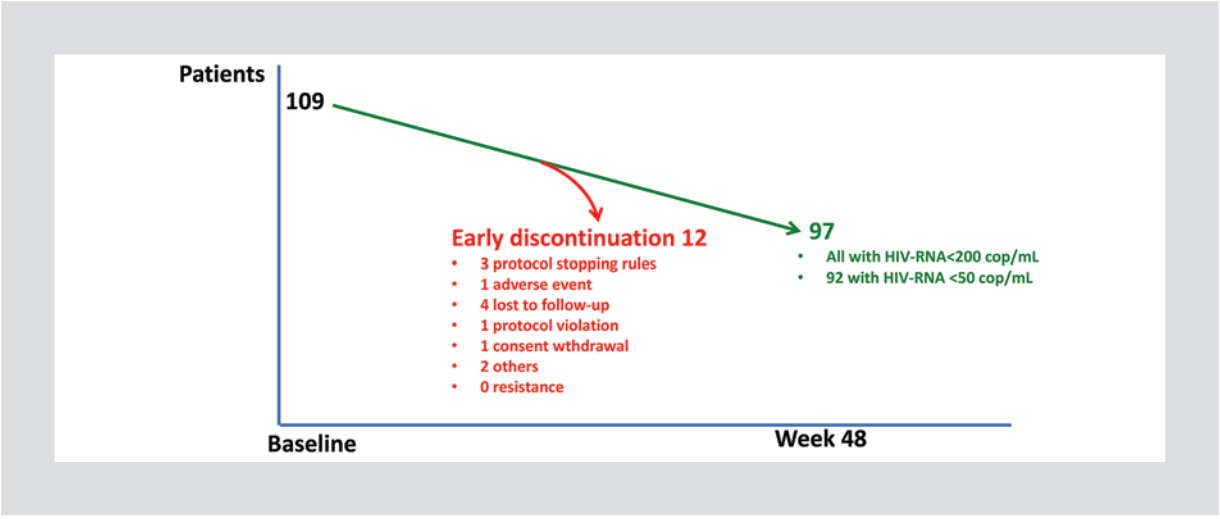

Figure 5. *Main results in the DIAMOND trial*[32].

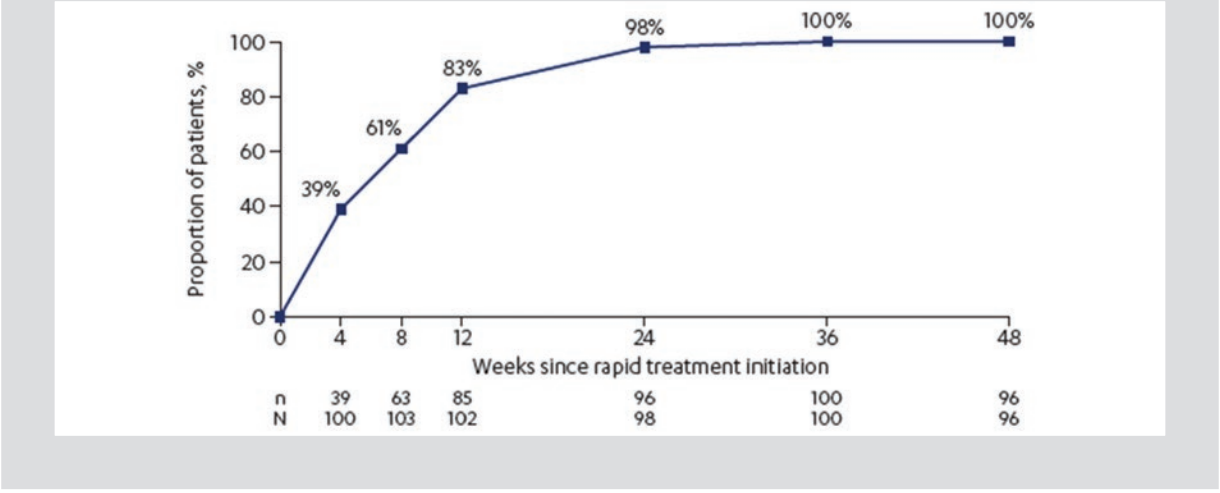

Figure 6. *Virologic response overtime in the DIAMOND study*[32] *(plasma HIV-RNA < 200 copies/mL; observed analysis).*

Interestingly, individuals with baseline moderate liver enzyme elevations normalized hepatic enzymes values following initiation of ART, most likely reflecting abolishment of inflammatory phenomena in the gut–liver axis associated with uncontrolled HIV replication.

In summary, the DIAMOND trial is the first Phase 3 study that has used a STR in a rapid initiation model of care. Overall, 89% of patients continued D/C/F/TAF ART through week 48 and rates of viral suppression were very high, ranging from 84% to 96%. Early in the study, a high proportion of patients achieved HIV-RNA <200 copies/mL (>80% of patients by week 12), which may help prevent HIV-1 transmission to uninfected individuals.

No patients discontinued due to lack of efficacy and none experienced virological failure. No patients discontinued treatment due to screening/baseline resistance results and none were eligible for post-baseline resistance testing. Overall, D/C/F/TAF was well tolerated and only one patient discontinued due to adverse events. Upon receipt of baseline laboratory results, three patients discontinued due to safety stopping rules.

The mean total HIV Treatment Satisfaction Questionnaire status score approached the maximum of 60 at week 4 and remained high through weeks 24 and 48, indicating high levels of patient satisfaction (overall 98%). These findings, together with the demonstrated efficacy, high barrier to resistance, safety profile, and convenience of the D/C/F/TAF STR, suggest that Symtuza® should be considered as a recommended treatment option in rapid initiation models of HIV care[32,33].

"Test and Treat" in special patient populations

Acute HIV infection

Rapid-start ART may provide unique benefits in acute (primary) HIV infection[34]. Acute infection confers greater risk of onward HIV transmission than chronic infection[35,36]. Consequently, rapid-start ART could reduce both individual viral load and community viral load, through its impact on onward HIV transmissions[37,38]. Early ART initiation may also benefit those with symptomatic primary HIV by arresting a rapid CD4 decline, compared with the decline seen in people with asymptomatic HIV infection[39,40]. In addition, in primary HIV infection, initiating ART may attenuate inflammation and reduce immune activation, compared with initiating ART when infection is chronic but CD4 counts remain high[39].

Pregnant women

In May and June 2018, the United States FDA and the European Medicines Agency, respectively, issued warnings on the use of dolutegravir and darunavir/cobicistat as HIV treatment of pregnant women[41]. The reasons for these warnings differed for each drug.

For dolutegravir, a large observational study detected a 0.9% risk of neural tube defects in infants delivered by women receiving the drug around conception or early in the first trimester of pregnancy. This was considered a substantial risk relative to 0.1% observed with other antiretrovirals[42]. This observation led to recommend that dolutegravir should only be used in adolescent girls and women of childbearing potential together with consistent and reliable contraception[41]. Exposure during the first trimester might impact embryo organogenesis and result in teratogenicity.

For darunavir/cobicistat, the warning in pregnancy derived from the recognition of an average reduction in plasma darunavir concentrations of roughly 50% during pregnancy compared to postpartum[43]. Cobicistat and ritonavir levels decrease by 50-60% during pregnancy, possibly leading to reduced boosting effects. This led to FDA label changes for all cobicistat boosted antiretrovirals in October 2018, indicating that these should not be used in pregnancy due to substantially lower exposure to antiretrovirals during the second and third trimester of pregnancy[44]. If darunavir is required during pregnancy, 600 mg dosing coformulated with ritonavir 100 mg (Prezista®) can be used.

Summary

The achievement of UNAIDS 95-95-95 goals by 2030 with <200,000 new HIV infections per year requires renewed efforts and innovative strategies since globally HIV rates are declining less rapidly than desired. Whereas providing antiretrovirals to uninfected persons at risk as PrEP have shown to reduce new HIV infections in a subset of individuals, mostly MSM living in rich countries, most new HIV infections worldwide occur outside this context, largely from persons unaware of their HIV-positive status and following heterosexual contacts.

Rapid initiation models of HIV care have demonstrated to maximize viral suppression and retention in care. The DIAMOND trial is the first Phase 3 study that has used a STR in a rapid initiation model of HIV care[32]. Overall, 89% of patients continued D/C/F/TAF through week 48 and rates of viral suppression were very high, ranging from 84% to 96%. Furthermore, early in the study, a high proportion of patients achieved undetectable viremia (>80% of patients by week 12), which may help prevent HIV-1 transmission to uninfected individuals. Thus, at this time, D/C/F/TAF is the only regimen that has demonstrated high efficacy rates when used as empirical ART in test-and-treat strategies.

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